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GERM CELLS AND SOMATIC CELLS[1]

LEO LOEB

RESULTS obtained in the field of experimental pathology and especially in cancer research have an important bearing on certain problems of general biology. In the following I wish to consider connectedly some of these facts from this point of view.

I. A sharp distinction between germ cells and somatic cells has become clearly established, especially through the writings of Nussbaum and Weismann. More recent results which demonstrated that the differentiation of germ cells from the somatic cells at a very early stage of embryonic development and their non-participation in the formation of somatic tissues exists in various species, tended to emphasize this sharp distinction between somatic and germ cells.

Weismann[2] especially insisted on the radical difference between germ cells and somatic cells, inasmuch as he attributed potential immortality to the former and only a temporary existence to the latter. And Weismann regards this difference as essentially founded in the structure of both kinds of cells and fundamentally connected with the functioning of the somatic cells; this difference was obtained through selective processes as an adaptation in the struggle for existence. He does not regard the death of somatic cells as an accidental occurrence due to unfavorable conditions which it might be in our power to change, but as an inherent characteristic of somatic cells. He mentions, though casually, that the life of the cock's comb might be prolonged by grafting it on another fowl—but only to dismiss this idea as having no important theoretical bearing. R. Hertwig[3] also regards the death of the somatic cells as unavoidably determined by their organization which precludes necessary readjustments.

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[1] From the Department of Pathology, Barnard Free Skin and Cancer Hospital, St. Louis.

[2] A. Weismann, ''Ueber Leben und Tod,'' Jena, 1884; ''Ueber die Vererbung,'' Jena, 1883.

Minot[4] likewise held the life of somatic cells to be limited in duration and he ascribed this limitation to changes in cell structure, leading to a differentiation of the cytoplasm during the process of life; a change which he designated as cytomorphosis.

Within the last 14 years certain facts have been established which are contrary to this conception of a radical difference between germ and somatic cells as far as their potential immortality is concerned. Experimental investigations in tumor growth have furnished these facts. Before we state these results we have first to consider, how far tumor cells can be regarded as somatic cells. We consider here malignant tumors (cancers). They originate at various parts of the body, often under the influence of long-continued irritation. In many cases we can, if we obtain sufficiently early tumors, trace the transformation of the normal into the abnormally proliferating (tumor) tissue. This has been, as was to be expected, especially observed in the case of superficial cancers, where early stages of tumors are most likely to be encountered, for instance, in cancers of the skin, of certain mucous membranes, but also occasionally in internal cancers as in those of the stomach. In such cases the cancer cells are undoubtedly the offspring of ordinary somatic cells. There are, however, tumors, so-called teratomata, which in all probability take their origin in the germ glands and other parts of the body from parthenogenetically developing ova. But while these latter tumors do not originate from somatic, but from germ cells, the tumor cells themselves are no longer germ cells, but somatic cells in the same sense as the ordinary tissue constituents which also are derived from germ cells. We can therefore without doubt regard tumor cells as a kind of somatic cells.

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[3] R. Hertwig, *Biol. Centralblatt,* Bd. XXXIV, No. 9, 1914.

[4] C. S. Minot, "The Problem of Age, Growth and Death," New York, 1908.

One of the most characteristic properties of cancer cells is their ability to grow after transplantation into other animals of the same species. This applies not to all, but to a certain number of spontaneous cancers; the majority of spontaneous tumors are not transplantable into other individuals of the same species. They grow, however, usually after transplantation into the same individual in which they originated. There does not exist as far as their origin is concerned any essential difference between these two kinds of cancers—those transplantable and not transplantable into other individuals. The cancers used in experimental tumor investigation take their origin from somatic cells; but it appears some are less sensitive to the difference in the chemical composition of the body fluids which exists between different individuals of the same species than others, and those less sensitive can be transplanted, while others can not.

In those tumors which are transplantable, relatively few tumor cells give after inoculation into other animals origin to the new tumors, and the tumor cells after the first transplantation not rarely multiply with greater vigor than they did in the original animal, an effect caused, as I could show, through the stimulating influence of the cutting and otherwise manipulating the tumor cells. In each animal therefore there are produced many successive generations of tumor cells, and after transplantation into another individual each surviving cancer cell produces again new generations. Consecutive transplantations into many individuals have been carried out with the same tumor. The potential proliferative power of the cancer cells is therefore enormous. It is, however, not so much the intensity of the proliferative power of the tumor cells which we wish to consider as the potential duration of their life. It has been shown that epithelial, as well as connective tissue tumors can be transplanted through many generations and can survive for a long time the animal in which the tumor originated. Thus I was able to transplant the connective tissue cells of a rat sarcoma through forty successive generations of animals, and it was merely the result of accidental bacterial infection due to the unfavorable conditions under which the work had to be carried out which caused the ultimate death of the propagated cells.

An epithelial tumor found by Jensen in a mouse has been propagated in various laboratories through a period of almost fifteen years, and another epithelial tumor of the mouse we have been propagating in mice for a period of seven or eight years, without any sign of diminishing vitality in the propagated cells being noticeable.

In all these transplantations of tumor cells, be they of connective tissue or epithelial origin, it could be shown that the peripheral cells remain alive and from these surviving cells the cell growth starts. These observations suggested to me in 1901 the conclusion that tumor cells may have a potential immortality in a similar manner as germ cells,[5] and inasmuch as tumor cells are only modified somatic cells, I furthermore concluded that the same statement holds good in the case of somatic cells.[5] Further experiences in the field of experimental tumor investigation during the following years confirmed this conclusion and permitted its enunciation with greater definitiveness.[6] The potential immortality of the somatic cells of course can only be made probable, it can never be definitely proved, inasmuch as our experience merely deals with finite periods. But the same restriction holds good in the case of the germ cells in which the potential immortality is likewise merely a strong probability and not a definitely proven fact.

Weismann believed that protozoa are in the same sense potentially immortal as germ cells, in contradistinction to somatic cells which do not possess potential immortality. Some facts were, however, discovered which, according to the interpretation given them, seemed to contradict Weismann's conception. Thus Maupas found that various kinds of infusoria did not propagate by fission indefinitely, but that a sexual process, conjugation, was necessary at certain times, and Calkins showed that there were regular periods of depression, and while a spontaneous recuperation from the effects of certain depressions could take place and in still other cases artificial stimulation would aid the animals in overcoming the critical periods, at other times depressions proved fatal without an intervening conjugation. Woodruff, however, by choosing conditions of environment more in accordance with the conditions found in nature, could keep a strain of *Paramæcium* apparently indefinitely alive without any intervening periods of copulation being required. This seemed to point to a potential immortality of protozoa in the sense of Weismann. Recently, however, Woodruff and Erdmann[7] found that the recovery from depression which takes place is accomplished through nuclear changes comparable to, but not identical with, those observed during copulation. This seems in some respects to agree with R. Hertwig's previously enunciated theory according to which depressions and senility in cells are due to a disproportion between the nuclear and cytoplasmic material, and that recovery from such unfavorable conditions depends upon the reorganization of the nucleus, essentially consisting in a diminution of the mass of the latter. Inasmuch as in metazoa—he concluded, further—such a rearrangement between nuclear and cytoplasmic masses can only take place in the case of germ cells, but not somatic cells, only germ cells are immortal, while somatic cells are necessarily mortal. While Weismann regarded the unavoidable mortality of the somatic cells as a secondary acquisition, the result of a process of selection, the death of somatic cells being of advantage to the propagation of the race, Richard Hertwig[8] regards the death of somatic cells as inherent in their structure, which precludes the possibility of nuclear reorganization of the cell necessary for continued life. In a somewhat related way, Minot considers, as mentioned above, the death of somatic cells as inevitable and as the result of cytomorphosis, which means the relative increase in size and differentiation of somatic cells during life. In this connection it is interesting to note that while R. Hertwig considers (in protozoa primarily, but secondarily also in other cells) an increase in the size of the nucleus—the result of the activity of the cells—as the cause of functional disturbances leading to senility, Minot on the other hand connects senility with a relative decrease in the size of the nucleus and an increase in the mass of the cytoplasm. Now as far as the protozoa are concerned, the controversy does not seem to concern so much the potential immortality of these organisms as the problem as to whether the individual protozoon corresponds to a germ cell or to a somatic cell of a metazoon, or whether it partakes of the character of both. There can be little doubt that individual protozoa possess potential immortality, a conclusion which would not be invalidated through a loss of certain parts of the protozoon body at certain periods of its life cycle.

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[5] "On the Transplantation of Tumors," *Jour. Medical Research*, Vol. VI, No. 1, 1901, p. 28; *Virchow's Archiv*, Bd. 167, 1902, p. 175.

[6] "Tumor Growth and Tissue Growth," *Am. Philosophical Society*, XLVII, 1908, and at other places.

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[7] *Biol. Centralblatt*, Bd. 34, August, 1914, p. 484.

[8] *Biol. Centralblatt*, Bd. XXXIV, 1914, No. 9.

We may therefore conclude that all three kinds of cells, protozoa, germ cells, as well as certain somatic cells of metazoa, possess a potential immortality.

Tumor cells are somatic cells in which such secondary changes leading to a cessation of proliferation as take place under certain conditions in all the individual cells in some kinds of somatic tissues, are affecting only a certain number of cells. In the case of some somatic cells, as, for instance, those of the epidermis, it is evident that the secondary changes in structure and metabolism, which lead to a cessation of proliferative power, are due to unfavorable conditions of blood-supply. What Minot calls cytomorphosis can therefore in this case be referred not to necessary transformations inherent in the cells, but to unfavorable environmental conditions into which the cells are placed as a result of their multiplication. Such secondary degenerative changes take place also in tumor cells under similar defective conditions of blood-supply. Here also degenerative changes entail a cessation of proliferation in a similar manner as in ordinary tissue cells. While farther away from the blood-vessels the tumor cells degenerate and die, near the blood-vessels they continue to live and to multiply.

While from a theoretical point of view, therefore, the question as to the potential immortality of somatic cells has through the experiments on tumor cells been answered in a decisive manner, it was nevertheless of interest to extend these investigations to ordinary tissues. Such investigations we undertook in the course of the last eight years, and while certain obstacles were encountered, which prevented the continued life of ordinary tissues, the results were of interest in giving an insight into some of the conditions which determine the growth, life and death of somatic cells. These investigations have shown that if tissues are transplanted into another individual of the same species, under the influence of the constitution of the body fluids, which differs in different individuals of the same species, the metabolism in the transplanted tissues is interfered with as shown, for instance, in pathological differences in pigmentation seen in black skin of the guinea-pig after transplantation into other animals of the same species. After transplantation of pigmented skin into the same individual in which it originated, such pathological changes do not occur. As I have previously pointed out, a certain adaptation exists between the tissues and body fluids in animals of the same species, and even between the tissues and body fluids of the same individual. Thus it comes about that the interaction of tissues and body fluids of the same species leads to different and less toxic products than those produced through the interaction of the body fluids of one with the tissues of another species. Even the interaction of tissues of one animal with the body fluids of another animal of the same species leads to more toxic products than the interaction of body fluids and tissues of the same individual. In the latter case toxic products, interfering with the life of normal tissues, are not produced, while in the former cases such products acting directly or indirectly are formed. As an illustration of such a specific relationship between body fluids and tissues, I cited the specifically adapted effect which tissue coagulins exert on the constituents of blood plasma.[9]

Now as the result of these differences in metabolism induced through the differently constituted body fluids the lymphocytes begin to invade the transplanted tissues, and the invading connective tissue does not preserve, as it does after auto-transplantation, its young and cellular state, but produces fibrous bands which contract around the parenchyma after homoiotransplantation, and thus exert pressure. Both connective tissue and lymphocytes destroy thus the homoiotransplanted tissue, while they usually spare the autotransplanted tissue the metabolism of which is normal. In the case of certain tissues, as, for instance, kidney, however, even after autotransplantation into the subcutaneous tissue the metabolism of the transplanted cells becomes abnormal under the abnormal conditions under which they now live, and here the lymphocytes and connective tissue destroy, therefore, even the autotransplanted tissue, although at a later date than the homoiotransplanted kidney tissue.

The fitness of a tissue in an individual determining its power to live or to grow depends, therefore, on two factors: (1) on the specific adaptation existing between tissues and body fluids, and (2) on the way in which various substances are carried to the tissue. A perfect nutrition implies the carrying of the food substances to the tissues in the normal way through blood-vessels. It is probable that on the intact relations between capillary endothelium and parenchyma cells depends such a sifting of various food substances and waste products as is best suited to the normal metabolism of the cells. If, as in the case of the kidney tissue, this mechanism is disturbed, abnormal substances are produced notwithstanding the specific adaptation existing in this case between tissue cells and body fluids after auto-transplantation. And it seems that a perfect fulfilment of the second requirement might even be able to overcome a deficiency in the first condition, the specific adaptation between tissues and body fluids. This seems at least to be the case, whenever a kidney is successfully transplanted into another individual of the same species and lives here for a long period of time.

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[9] "Immunity and Adaptation," *Biol. Bulletin*, Vol. IX, 1905, p. 141.

A peculiar resistance to foreign body fluids is apparently shown by the germ cells. They represent in reality individuals residing in a host organism of the same species. In this case the host organism is nearly related to but not identical with the individuality of the germ cells. In some respects we have, therefore, here a condition comparable to one existing after homoiotransplantation of tissues. And still the germ cells do not show any signs of injury. There is, therefore, in germ cells as yet lacking that substance which has a specific affinity to certain parts of the body fluids, or through their situation the germ cells are somehow protected against the injurious influence of these substances.

Thus it comes about that through transplantation into other individuals of the same species the potential immortality of the ordinary tissues can not be demonstrated. This applies to the tissues investigated so far.[10] However, it is quite possible that we may yet find that in the case of certain tissues the life may be permanent even after homoiotransplantation. It was furthermore thinkable that through serial transplantation, retransplanting the tissue at an early date before the lymphocytes and connective tissue had had a chance to seriously injure it, better success could be obtained. In the case of the skin I have undertaken such serial transplantations some years ago; our investigations have, however, in this case shown that it was not possible to retransplant this particular tissue indefinitely;[11] these experiments ought to be extended; especially might it be of interest to use the direct descendants as hosts for the tissues of the parent. It is to be expected that the quality of the parents which makes the body fluids suitable for their own tissues might make them likewise suitable for certain of their offspring. Such experiments I began some time ago and I expect to continue them if opportunity should present itself.

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[10] Leo Loeb u. W. A. F. Addison, *Arch. f. Entwicklungsmechanik*, Bd. XXVII, 1909, p. 73; Bd. XXXII, 1911, p. 44. Max W. Myer, Bd. XXXVIII, p. 1, 1913. Llewellyn Sale, Bd. XXXVII, 1913, p. 248. M. G. Seelig, Bd. XXXVII, 1913, p. 259. Cora Hesselberg, *Journ. Experimental Medicine*, Vol. XXI, 1915, p. 164.

The growing of tissues in culture media, which excludes attack on the cells by connective tissue and lymphocytes, may also serve the same purpose and quite recently has been used through a larger number of generations. But, as stated above, we have in these experiments merely to deal with an attempt to confirm the potential immortality of the somatic cells which had in principle been established through previous investigations on the life of tumor cells.

While thus various kinds of tissues of an organism have the potentiality of an immortal life, separated from the organisms to which they belonged, the organism as a whole invariably dies and with it its component tissues. This is evidently due to the interdependence of various parts of an organism and to the death of certain sensitive cells, especially the ganglia cells of the central nervous system. We might therefore be inclined to conclude that these ganglia cells do not possess the potentiality of immortal life. But even in the case of the ganglia cells, which are of such significance for the life of the organism as a whole, we can at present not deny the possibility that they also may have the potentiality of immortality and that they merely succumb under the influences of certain injurious conditions arising in the organism. On the other hand, fully developed ganglia cells have apparently lost the power to multiply; they are furthermore sensitive to certain insults to which other tissues show resistance. Thus the unfavorable condition prevailing during the process of transplantation into another organism and directly afterwards seems to be sufficient to cause the death of certain ganglia cells when other tissues would survive. But neither of these facts prove that under favorable conditions very much differentiated cells, like ganglia cells, might not have the power to live indefinitely, although they have lost the power to multiply. Sensitized connective tissue cells of the uterus may after transplantation into the same or another individual in which corpus luteum substance is circulating grow very energetically and produce placentomata, while after transplantation of fully developed deciducomata no further growth can be obtained and all or almost all the cells die. Here also the fully "differentiated" cells have lost the power to multiply and at the same time they have apparently become more sensitive to the effect of injurious influences than young and yet undifferentiated predecidual cells of the uterine mucosa.

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[11] Leo Loeb, *Archiv. f. Entwicklgsmch.*, Bd. XXIV, 1907, p. 638.

But here we can observe that some strands of fully differentiated placentoma tissue may survive even under those unfavorable conditions—without, however, resuming growth or returning to the undifferentiated condition—namely, such strands of tissue as are situated under the best environmental conditions, in close proximity to the host tissue, at places most accessible to the foodstuffs or oxygen supplied by the circulating blood or by the peritoneal fluid. This suggests that even much differentiated cells which have lost their power to propagate may still have the power to live, when kept under favorable conditions, and that their death is the result of unfavorable environmental influences. Thus we must at least admit at the present time the possibility that also the ganglia cells, while they do no longer multiply, may still possess a potential immortality; that cellular differentiation precludes the latter possibility has as yet not been demonstrated. We must therefore sharply distinguish between the power of cells to grow and their power to live; while the former seems to be destroyed through differentiation —at least in some cases—the latter may still exist. In the case of other tissue cells we have it to a certain extent in our power through experimental conditions to prevent those changes which lead to differentiation and death; thus in the case of tumor cells through constant transfer into a new host we can enormously increase the number of as yet less differentiated cells on which the propagation depends by causing an intense multiplication of these tumor cells, many of which, if left in the same organism, would have undergone secondary degenerative changes. Through experimental means, viz., through the transplantation into different kinds of hosts the relative preponderance of propagation and differentiation of tumor cells can be varied. We furthermore know that through "chemical" sensitization combined with mechanical stimulation, the same effect can be produced, at least temporarily, in the connective tissue cells of the uterine mucosa. Under those conditions a large number of cells are induced to propagate and remain young while their offspring gradually change into fully differentiated cells. If we grant the possibility that differentiation of such cells as ganglia cells, while it entails loss of the power to propagate and greater sensitiveness to insults, does not necessarily mean the necessity to die, then the problem of prolongation of life would to a great extent depend upon the possibility of preventing injurious influences which at present disturb the function of ganglia cells from attacking these cells and causing their death.

II. The germ cells are potentially immortal, but this potential immortality can only be realized, if at certain periods certain changes take place within the cells, which concern especially the nucleus, phenomena consisting in maturation, followed by fertilization or parthenogenetic development. In a similar manner the observations of Woodruff and Erdmann suggest that at the time of depressions in the life of the protozoa, possibly similar nuclear phenomena take place at least in certain cases. We have seen that in the case of somatic cells there are also indications of the existence of potential immortality. The question may therefore be raised, whether similar periodic rearrangements of the nucleus, as in the case of the germ cells and protozoa, may not also take place in the case of the somatic, especially of tumor cells. Without considering any connection with the problem of the immortality of the somatic cells, Bashford, Murray and Bowen[12] stated on an empirical basis that in charting the number of successful inoculations of a mouse carcinoma in mice, in different generations and in different strains of the same generation, they noticed definite rhythmic variations in the number of successful inoculations, a maximum of successful inoculations in one generation being followed by a minimum in the succeeding generation. However, they also state that parallel strains of the same tumor did not show maxima or minima at the same time. Bashford, Murray and Bowen, in order to explain these observations, assumed that different parts of the same tumor show different degrees of growth energy at the same time; this would imply that such areas differing in growth energy at the same period are separated through transplantation; so that in one generation mainly energetically growing pieces are used for transplantation in the succeeding weakly growing pieces almost altogether, an assumption which does not appear very probable.

Calkins[13] held that there occur in succeeding generations not so much rhythmic variations in the number of successful transplantations as in the growth energy of the tumors. He compared these rhythmic variations with the rhythms observed by him in the case of *Paramœcium*. However, such rhythms were not noticeable in the mouse carcinoma which we have propagated for a number of years in our laboratory, as has been shown by Moyer S. Fleisher.[14] He furthermore shows that even in the case of those tumors, on the study of which Bashford and his collaborators and Calkins base their conclusion, it is very probable that the variations which these authors observed do not represent definite rhythms, but are, as far as their conclusions are not based on methods of determining the growth energy of tumors, not suitable for this purpose, in all probability merely the expression of the existence of a number of uncontrolled variable factors. Such factors are numerous and they may explain certain variations observed in growth energy and number of takes in transplantations undertaken at different times or in different mice. There exists, therefore, at the present time no evidence making even probable the existence of rhythms of growth and vitality in somatic cells comparable to those found in protozoa; neither have thus far been found in somatic cells indications of nuclear changes similar to those periodically occurring in germ cells and probably also in some protozoa and apparently bearing some relation to variations in growth and vitality in these cells. At present we must therefore reckon at least with the possibility that the immortality in somatic cells is not connected with rhythms in vitality and in nuclear changes of such a character as observed in the other two kinds of potentially immortal cells.

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[12] Bashford, Murray and Bowen, *Zeitsch. f. Krebsforschung*, 1907, Bd. 5, Heft 3.

[13] Calkins, *Jour. Exper. Med.*, 1908, X, 283.

[14] Moyer S. Fleischer, *Zeitschrift f. Krebsforschung*, Bd. 14, Heft 1, 1914.

III. External factors acting on an organism may exert an influence on its germ cells and here produce certain changes which may be transmitted to the following generations, and thus through a number of generations the offspring may show deviations from the type, although the character of the lesions appearing in different generations may not be identical. This has been observed as a result of the action of poisons such as lead and alcohol. Especially the extensive investigations of Stockard on the action of alcohol in guinea pigs demonstrate conclusively that defects appear through several generations. In the case of these injuries transferred to the offspring, it is doubtful whether and to what extent these inheritable defects are characteristic for a certain poison, or whether we have to deal with traumatisms which might be caused in a similar manner by many poisons or even by injurious physical agencies. There is some evidence tending to show that most diverse chemicals may influence embryonic development in a similar manner, that they may produce identical defects in the developing organisms. It seems to be otherwise in the case of certain external conditions which produce first changes in some somatic cells which on their part apparently induce such secondary changes in the germ cells that in the offspring, not exposed to the external conditions that affected the parents, again changes appear in some somatic cells similar to those produced in the parents through the external conditions. Such results were published by Kammerer. In the latter case the changes produced and transmitted to the offspring showed evidently a characteristic specific relationship to definite external conditions. Such a specific relationship is, as far as we can judge at present, lacking in the case of defects or deficiencies produced through the action of poisons.

I wish to report briefly on a change which my collaborators Moyer S. Fleisher, Miguel Vera and myself[15] have produced in somatic cells, a change which is transferable to the following cell generations and is therefore hereditary, and which, while it would be pronounced non-specific, if we should use ordinary criteria, can through the use of special methods be shown to possess a definite, characteristic relationship to the external factor that caused this change and must therefore be called specific. The observations on which these conclusions are based are briefly as follows:

If we inoculate mice with the mouse carcinoma used by us in our experiments and from the ninth to the fourteenth day after inoculation give on successive days four intravenous injections of such substances as colloidal copper or hirudin, a marked inhibition in growth takes place during the period of injection. The intensity of this inhibition varies in different cases and it is possible for us by using a combination of two substances to cause a retrogression of a considerable number of tumors. Now, if we inject daily from the second to the fifth day after inoculation mice with either of these two substances, tumor growth is not noticeably retarded through the injections. Tumors, in an early stage of development, are resistant to this inhibiting effect. If we now give four intravenous injections, one on each successive day, from the second to the fifth day, and later again to the same mice four injections from the ninth to the thirteenth day, the latter series of injections which had been effective in other animals not previously injected from the second to the fifth day, have now almost completely lost their efficacy. The mice have through the first set of injections become immune against the action of colloidal copper and hirudin as far as the effect of these substances on tumor growth is concerned.

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[15] Moyer S. Fleisher and Leo Loeb, *Jour. Exper. Med.*, Vol. XX, 1914, p. 503. Moyer S. Fleisher, Miguel Vera and Leo Loeb, *Jour. Exper. Med.*, Vol. XX, 1914, p. 522. Moyer S. Fleisher and Leo Loeb, *Jour. Exper. Med.*, Vol. XXI, 1915, p. 155.

We next inquired into the mechanism of this immunity, and especially were we concerned with the place where this immunity is produced. It was conceivable that this took place either in some organ of the injected animal or in the tumor cells themselves. The following experiments showed that both possibilities were realized: If we inject the mice on the four days preceding inoculation with tumor, immunity is produced, at least in the case of colloidal copper. This proves that some organ in the host animal contributes to the immunity, inasmuch as in this case the preliminary injections exerted their influence without having had a chance to act on the tumor cells. But the tumor cells themselves also become actively immune, as shown in the following manner: We inject animals with either colloidal copper or hirudin from the second to fifth day, and again from the ninth to the thirteenth day after inoculation. Two days after the last injection we used the tumors of some of the injected animals for reinoculation into a new set of mice. Nine to thirteen days after this second inoculation the mice belonging to the second set are injected with colloidal copper and hirudin, respectively. Now we find that these tumors also are almost entirely resistant against the effect of colloidal copper and hirudin, although in this case no preliminary injections had been given to the animals which are now the bearers of the tumors. It is therefore necessary to conclude that the tumor cells used for transplantation are in this case the sole bearers of the immunity, and that the tumor cells themselves have been actively immunized. From the latter experiments we may furthermore conclude that the immunity acquired by tumor cells is transferred to the following generations of tumor cells, and that therefore a hereditary transmission of a character acquired by somatic cells under the influence of external conditions takes place. The conclusion is based on the following consideration: The process of tumor inoculation consists in the transfer of a very small particle of tumor. Very soon after transplantation most of the transplanted tumor cells become necrotic and only a relatively small number of peripheral tumor cells remain alive. These very soon begin to proliferate, and through their proliferation give origin to the developing tumor. If therefore the tumors developing after transplantation in the new hosts are immune, the immunity must have been transmitted from the few cells remaining alive after inoculation to the new cell generations to whom they give origin. A fully developed tumor represents a combination of a large number of generations of tumor cells and it may be assumed that the later generations of tumor cells preponderate numerically very much over the earlier generations. Through how many generations of tumor cells this transmission of the acquired immunity can be propagated remains yet to be determined. From our preliminary experiments, which are, however, not yet definite, it appears not improbable that it extends at least through several series of transplantations.

Both colloidal copper and hirudin inhibit tumor growth. The sign by which we judge the effect of these substances is therefore essentially the same in both. We might thus be inclined to conclude that their action is identical and that likewise the immunity which they produce is the same; that animals having received preliminary injections of colloidal copper would therefore be immune not only against the action of colloidal copper but also against hirudin, and that those having received preliminary injections of hirudin would also be immune against colloidal copper. We wished to test this conclusion and undertook therefore experiments in which we immunized animals with one substance and examined later their immunity not only against the substance with which they were immunized, but also against the other substance. These experiments showed that animals immunized with colloidal copper are essentially only immune against the effect of colloidal copper, not of hirudin, and those immunized with hirudin are immune against hirudin, but not noticeably (very weakly, if at all) against colloidal copper. The acquired immunity is therefore a specific one. This specificity can be shown to exist if after preliminary injections given from the second to the fifth day after inoculation the immunity is tested through cross injections given from the ninth to the thirteenth day. It can also be demonstrated in the tumors transplanted into other animals after preliminary injections in the first set of animals. The specificity concerns therefore the immunity which is produced in the tumor cells and probably also the immunity in the organism of the injected animals. These investigations prove then (1) that an acquired immunity against the injurious action of certain substances can be localized in the cells concerned; (2) that this immunity can be transferred to later cell generations; and (3) that although the effect of two substances on the cells is apparently the same, the mechanism through which this effect is produced differs in the case of each substance, and that therefore the immunity produced against the injurious action of these substances is a specific one for the substances injected. We see therefore that in a similar manner as in germ cells an effect produced through an external agency can be transmitted to later generations; a transmission of changes produced through an external (chemical) agency may be transmitted to later generations also in the case of somatic cells. But the further results we obtained in the case of somatic cells suggest the question whether the lesion produced and transmitted in germ cells may not also be specific, although different chemicals produce apparently the same results. May there not in germ cells, just as in somatic cells, exist a difference in the mode of production of these lesions through the different substances and consequently a specificity in the acquired lesion, notwithstanding the apparently unspecific character of the lesion? Our work makes it possible that this question which seems of considerable theoretical interest may be solved in a similar manner as in the case of the somatic cells, viz., through testing the immunity produced through the action of chemical substances.

SUMMARY

1. It is shown that evidence similar to that which makes probable the potential immortality of protozoa and germ cells also exists in the case of somatic cells of metazoa. As far as the protozoa are concerned, the discussion does not, as seems to be assumed, concern their potential immortality so much as the question whether protozoa correspond to germ or to somatic cells of metazoa or represent perhaps a combination of both.

2. While in the case of tumor cells the potential immortality of somatic cells has been demonstrated as definitely as the character of the problem will ever permit, the difficulties standing in the way of a similar demonstration in the case of certain other somatic cells and the means of overcoming these difficulties are analyzed. It is particularly shown that chemical differences existing between the body fluids of individuals belonging to the same species are the basis of these difficulties, and that as a result of these differences the metabolism of cells in a new environment is modified in such a way that the behavior of connective tissue cells and of lymphocytes is altered, and that as a result of these alterations the death of the tissue is brought about where it could probably have lived indefinitely. Besides altering the character of the body fluids, transplantation of tissues furthermore has usually an additional injurious effect; it changes the way in which nourishment is carried to the transplanted cells, and this

may also lead to alterations in metabolism calling forth a destructive activity of connective tissue and lymphocytes. Thus there exist difficulties in the case of certain tissues in demonstrating through serial transplantation their potential immortality, in a similar manner as it has been demonstrated in the case of strongly proliferating somatic cells (tumor cells).

It is also shown that in the case of the germ cells which really represent a foreign individual within a host organism mechanisms exist which prevent these injurious agencies from becoming effective.

3. We must sharply distinguish between the power of cells to grow and their power to live. While the former seems to be destroyed through differentiation, the latter may still exist, and we can therefore at present not deny the possibility that even highly differentiated somatic cells may still possess the potentiality of immortal life.

4. While in the case of protozoa and germ cells definite cycles exist, manifesting themselves either through the occurrence of rhythmically occurring depressions of vitality or of typical changes in the nuclei, such cycles have so far not been demonstrated in the case of somatic cells, particularly of tumor cells.

5. In the case of germ cells external factors can produce certain changes, and these changes (not necessarily identical with those originally produced through the external factors) can be transmitted to the offspring. It is shown that in a similar way in the case of somatic (tumor) cells a transmission of characters acquired under the influence of external agencies to the succeeding cell generations may take place. It can be shown in the case of the somatic cells that apparently similar changes produced through different external agencies are really not identical, but specific. It is suggested that such a specificity of transmitted characters may also exist in the case of germ cells despite the apparent identity of changes produced through different external agencies.